

Antiepileptic drug research in Asia: Where do we go from here?

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Abstract

Efforts in clinical research of antiepileptic drug therapy in Asia have traditionally biased towards postmarketing surveillance studies. Although valuable in assisting the translation of regulatory trial data into everyday clinical practice, phase IV studies are inadequate in addressing the fundamental challenges facing drug treatment of epilepsy in Asia today. These issues include ways to reduce the treatment gap, a better understanding of the treatment outcome of epilepsy, pharmacology of antiepileptic drugs, genetic influence of drug response, and the prevention of epilepsy. It is hoped that strategic partnership between national governments, pharmaceutical industry, clinicians and patients may help more patients in Asia benefit from effective antiepileptic treatment and live more fulfilling lives.

INTRODUCTION

At least 9 new agents have been approved for the treatment of epilepsy since the late 1980s.¹ In this issue of the Journal, Ong *et al*² reported an open label study of topiramate, one of the new antiepileptic drugs (AEDs), as add-on therapy in a group of paediatric epilepsy patients in Malaysia, while Krishnan *et al*³ presented experience on the clinical use of several new AEDs in an Indian neuroscience centre. Both reports represent phase IV clinical studies and described the efficacy and tolerability of some of the new AEDs in clinical use among Asian populations.

Efforts in clinical research of AED therapy in Asia have traditionally biased towards such postmarketing surveillance studies. These studies are valuable in optimising the use of any newly introduced treatments since regulatory trials are primarily designed to satisfy licensing requirements and it is questionable whether their results can be readily extrapolated to clinical practice.⁴ This concern is perhaps particularly applicable to the new AEDs which tend to be investigated in highly selected patient samples over relatively short durations in phase III clinical trials.^{5,6} Another main reason for conducting phase IV studies in Asia is because most, if not all, of the currently available AEDs were initially studied in western populations. Local post-marketing studies can aid the adaptation of results from these phase III trials and can detect or highlight

adverse drug reactions of particular concern to the region. The relatively high incidence of fever among children given topiramate in tropical Malaysia reported by Ong *et al*² is a notable example.

However, phase IV studies are clearly inadequate in tackling the many unanswered questions and unmet needs in the management of epilepsy in Asia. Geographically, Asia is the largest among the continents. It is estimated to be inhabited by 3.8 billion people, which is over half the world's population⁷, distributed over 40 countries. The nations vary widely in both the "hardware" (geography, population size etc.) and "software" (levels of cultural and socio-economical development, health care systems etc.) aspects. Gross national income per capita differs over 140-fold between the richest and the poorest countries in the region.⁸ Such extreme diversities pose great difficulties in developing a uniform treatment standard across Asian countries. This article aims to give a personal view on the current major challenges facing the drug treatment of epilepsy in Asia. Possible research directions to address these areas are proposed.

TREATMENT GAP

Like the rest of the developing world, disparate availability of AEDs and "treatment gap" remain the two major problems in epilepsy management

in many poorer countries in Asia, particularly in the rural regions. An ILAE report in 1985 on the availability and distribution of AEDs in developing countries recognised that “older and less efficacious compounds ... are the only AEDs available to most patients, whereas newer and more efficacious compounds are either not available or restricted to a very limited number of cases”.⁹ Unfortunately, nearly 20 years after the publication of this report, not only does AED availability remain a major deficiency, a substantial proportion of patients in developing countries, including those in Asia, are still simply not being treated at all.¹⁰ For instance, a recent household survey in rural regions of China found that 63% patients with active epilepsy were not under treatment.¹¹

It is tempting to attribute the treatment gap solely to the expensive costs of AEDs since epilepsy is not included in most national health care plans in Asian countries. However, it has been estimated the average net cost of treating a patient with phenobarbital for a year is only US\$2.6.¹² Therefore, the reasons for the large treatment gap and disparate usage of AEDs are likely to be multifactorial, including such socio-cultural and political factors as treatment-seeking behaviour, health care provision system, availability of expertise, reliability of quality drug supply, social stigmatisation etc.¹³ On an infrastructural level, studies should be performed to investigate the local causes and ways to reduce the gap.

NATURAL HISTORY OF TREATED EPILEPSY

Understanding the natural history of epilepsy has fundamental implications for devising a rational approach to the management of epilepsy.¹⁴ Recent long-term outcome studies in western populations of newly diagnosed patients represent an important step towards delineating the history of epilepsy in response to AED therapy.^{15,16} Similar prospective data are lacking in Asia. It is possible that the natural history may vary between regions in the world due to different underlying aetiologies, syndromic classification, treatment strategies, or even genetic factors. In addition, there has been a growing emphasis on psychosocial outcomes in assessing effectiveness of AED therapy.¹⁷⁻¹⁹ However, many psychometric tests and quality of life scales have not been validated in the native languages of non-English speaking populations, severely limiting their use.

Prospective long-term outcome projects in Asia may be incorporated into health service development programmes or as an extension of the ongoing demonstration projects that are being implemented as part of the Global Campaign Against Epilepsy in various countries across the developing world.²⁰ The Global Campaign Against Epilepsy is a joint initiative of the International League Against Epilepsy, International Bureau for Epilepsy and World Health Organization to bring epilepsy “out of the shadows” and improve the care of epilepsy patients around the world.²¹ The outcome projects could help solve the pressing need to devise cost-effective and sustainable treatment programmes for epilepsy in the less developed areas in the region, while providing much needed long-term outcome data and evaluating factors that influence the response to AED treatment. Locally validated psychometric tests and quality of life scales should be developed to assess the tolerability of AEDs objectively. Outcome measurements including educational, employment and family issues would allow assessment of the real impact of AED treatment upon socio-economical functioning of patients with epilepsy in Asia.

PHARMACOLOGY AND PHARMACOGENETICS OF ANTIEPILEPTIC DRUGS

The regulatory trials of most, if not all, of the new AEDs were performed in western countries.²² However, as eluded above, a number of factors may lead to variation in pharmacokinetic and pharmacodynamic response between the western and Asian populations, resulting in differences in efficacy and tolerability. A notable example is the response to treatment with phenobarbital, which is reputed to be exceedingly neurotoxic in some trials performed in industrialised countries²³, but is well tolerated and highly efficacious when used in Asian patients.²⁴

There has been growing attention on the potential influence of genetic variants on drug responsiveness.²⁵ Traditionally, the study of pharmacogenetics in epilepsy has focused on the effects of polymorphisms of the drug metabolizing genes on susceptibility to drug toxicity. Variants of genes encoding the cytochrome P450 (CYP) enzyme system, which metabolises the established AEDs, have been extensively studied.²⁶ Polymorphisms of CYP2C9 and 2C19 have been reported to affect the clearance of phenytoin²⁷ and phenobarbital²⁸, respectively.

Recent attention has turned to the potential effect of genetic variations on drug efficacy. For instance, there is growing evidence to suggest that cerebral access of certain AEDs is limited by drug transporters at the blood-brain barrier, the prototype of which is P-glycoprotein.^{29,30} A C3435T polymorphism of the *ABCB1* (or *MDR1*) gene, which encodes P-glycoprotein, has been reported to affect the level of protein expression and to be associated with resistance to AED therapy in epilepsy patients.³¹ A Brazilian study showed that a variant allele Asn171Ser of the cellular prion protein gene was more common in patients who underwent surgery for refractory mesial temporal lobe epilepsy associated with hippocampal sclerosis than the general population, and conferred a poorer outcome after temporal lobectomy.³²

The frequency of genetic polymorphisms varies markedly between ethnic groups. Among 42 examples of polymorphisms of drug metabolizing enzymes, 28 showed variation in their frequencies between different ethnic populations.³³ Similarly, the frequency of the *MDR1* C3435T polymorphism exhibits wide ethnic variation, such that 65% to 83% African blacks express the T/T genotype, but only around 25% white people do so, while the frequency among Asians lies somewhere in between.³⁴

Population-based pharmacogenetic studies are needed to determine whether this variation results in differential response to AED therapy, both in terms of efficacy and neurocognitive side effects, across different ethnic groups. Such studies may be incorporated into the prospective treatment outcome projects, providing the opportunities to assess how knowledge of the relevant genotype might influence clinical outcomes and to derive reliable estimates of positive and negative predictive values. Since the effects of a given polymorphism may be influenced by the genetic background, and the pattern of linkage disequilibrium varies considerably across populations, pharmacogenetic studies should be performed in the individual populations to generate locally applicable data.

Apart from genetic factors, differences in body size, composition, underlying aetiology of epilepsy, and environmental factors may also potentially affect the efficacy and tolerability of AEDs between patients in different regions of the world. Deficiency in local data on the pharmacokinetic and pharmacodynamic properties of AEDs in Asian patients has hampered the extrapolation of results from studies conducted

in other populations. There is a need for clinicians and the pharmaceutical industry to appreciate the essential value of local clinical trials for optimising the use of AEDs, including dosing, titration regimen, patient selection etc. To maximise relevance and applicability, these local trials should be carried out from as early as phase I in the development of new agents, rather than waiting until the post-marketing stage.

ANTIEPILEPTOGENESIS

The prevention of the development of epilepsy (epileptogenesis) and resistance to medical therapy (pharmacoresistance) have been recognised as two of the major challenges in epilepsy treatment today.³⁵ It is likely that separate but overlapping factors are operating in these two processes, ranging from molecular to macrostructural levels.³⁶ Epileptogenesis refers to a variety of progressive biochemical, anatomic, and physiologic changes that occur during a “silent interval” after an initial CNS insult, eventually leading up to recurrent spontaneous seizures i.e. epilepsy. Intervention during this “silent interval” to people at risk is the rationale behind the drive to develop “anti-epileptogenic” therapy.

Successful development of anti-epileptogenic agents depends on an understanding of the cascade of dynamic biological events that alter the balance between excitation and inhibition in neural networks, which might vary depending on the complex interactions between the genetic makeup of the individual and environmental factors. In particular, the mechanisms responsible for epileptogenesis might be affected by the nature of the initiating insults i.e. aetiologies²⁹, which vary widely according to geographic location.³⁷ While cerebrovascular disease is the most common identifiable cause of epilepsy in developed countries, a past history of CNS infections is more prevalent in the developing world. For instance, neurocysticercosis, widespread in Asia, is estimated to be the cause of epilepsy in up to 50% of Indian patients presenting with partial seizures.³⁸

Therefore, although clinical prevention trials using existing AEDs (mostly the established agents) have so far failed to demonstrate an antiepileptogenic effect among patients with risk factors such as head injury or craniotomy,³⁹ their results might not be directly applicable to populations with other CNS insults that predispose to epilepsy. While efforts are devoted to identify new molecular targets and develop more

innovative models and agents, prevention trials using existing AEDs targeting patients with locally prevalent risk factors among Asian populations may be considered.

CONCLUSION

As we move further ahead in the 21st century, there is a need for investigators in Asia to widen the scope of AED research to tackle the many pressing local challenges, including ways to reduce the treatment gap, a better understanding of the treatment outcome of epilepsy, pharmacology of AEDs, genetic influence of drug response, and the prevention of epilepsy. The Asian-Oceanian Declaration on Epilepsy in 2000 recognised the urging need to promote and support research in the region into the basic processes, clinical aspects, and psychosocial consequences of epilepsy.⁴⁰ It is hoped that strategic partnership between national governments, pharmaceutical industry, clinicians and patients may help fulfil this objective so that more patients in Asia can benefit from effective antiepileptic treatment and live more fulfilling lives.

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